EXTENDING THE SHELF LIFE OF CRITICAL "WAR RESERVES" MEDICAL MATERIEL USING THE FDA/DOD SHELF LIFE EXTENSION PROGRAM

Introduction

To assure preparedness for war or other contingencies, the Department of Defense (DoD) maintains significant pre-positioned stocks or war reserves of critical medical materiel. All drugs possess finite, labeled expiration dating. Routine replacement of them can be quite costly for the DoD and the taxpayer. To reduce overall costs, and taxpayer burden for these stocks, the DoD participates in cooperative product evaluation program with the U.S. Food and Drug Administration (FDA).

The FDA/DoD Shelf Life Extension Program is a key component of the Medical Readiness Strategic Plan (MRSP) as developed by the Office of the Secretary of Defense for Health Affairs and the Military Medical Departments in response to Congressional concern over the conservation of military medical resources. The program's focus is to defer drug replacement costs for date sensitive pre-positioned and war reserve stocks by extending their useful life. The following organizations participate in the program: the FDA, the Defense Medical Standardization Board (DMSB), Army, Navy, Air Force, Marine Corps, Defense Supply Center-Philadelphia (DSCP) and the Department of Homeland Security's Strategic National Stockpile (SNS). The DSCP manages the medical materiel for the DoD to include the depot system. The SNS manages our Nation's medical materiel stocks for responding to Chemical, Biological, Nuclear/Radiological, or conventional weapon terrorist attacks on the American people. The SNS maintains its own "pre-positioned stocks" and benefits from the program experience of the DoD.

The FDA evaluates candidate materiel for shelf life extension by testing samples submitted from the SLEP Participates. The DMSB coordinates the program and acts as the single interface between the SLEP Participates and the FDA. The SLEP Participates funds the program, manage their portions of the program, and receive the benefit of deferred materiel replacement costs. The Shelf Life Extension Program (SLEP) assures only safe and effective drugs are provided to personnel during war or other contingencies.

History

Prior to the introduction of the program, the Services were investing significant funds in replacement costs for pharmaceutical products of potency dated pre-positioned stocks, war reserves and depot stocked pharmaceuticals. Replacement costs for these drugs in 1986 totaled $2.5 million. One of the methods suggested to limit expenditures and defer drug replacement costs for this materiel was testing for potential extension of their useful life.

In July of 1985, representatives from the Air Force Surgeon General's Office and the FDA met to determine the feasibility of testing drugs for extension. An agreement was reached at this meeting to establish a pilot project for testing. The Air Force identified a list of items

representing stock costing $3,000 or more and within 12 to 18 months of its expiration. The FDA screened the list and established test protocols for 56 of the items. Samples of the items were sent to the FDA for testing. After 8 months of testing, the final results exceeded expectations. A total of 80% of the items were tested, and 84% of all lots tested, were extended. Although the FDA was conservative in their estimates, some of the tested items were granted extensions of up to 3 years beyond their initial expiration date.

In January of 1986, an interagency agreement was signed forming the FDA/DoD Shelf Life Extension Program (SLEP). The DMSB was tasked as the Quad-Service, DoD focal point for the program. Testing of items submitted by the Services and DSCP was not started until fiscal year (FY) 87. By FY 91, the program had grown enough for the FDA to increase dedicated program resources (facilities and personnel) to support requirements for new as well as retest projects.

The program has changed significantly over time, as pharmaceutical industry practices and knowledge about product safety and stability have evolved. Today the SLEP is geared towards the testing of "military significant" products, those that are either military-unique, possessing no commercial (non-DoD) market, or those drugs for which the DoD procures such large quantities for pre-positioned stocks and war reserve requirements that vendors are unwilling to accept them for credit upon expiration.

FDA Testing

The FDA is the independent evaluator and proponent for quality control of medical materiel, performing all required testing of items entered into the FDA/DoD SLEP. The FDA uses the U.S. Pharmacopoeia or the original manufacturer's test data on each item to establish a protocol for testing. Accelerated testing (also called stress testing) is the method used most often to predict the extension period. The accelerated testing protocols are designed to increase the rate of chemical or physical degradation of the drug substance by using exaggerated storage conditions. Each item is "stressed" (placed in chamber which maintains a temperature of 50 degrees centigrade and 75% humidity) for 60 days. The potency of the stressed samples is compared with the standard for each item, and using the comparison, the FDA estimates the extendable life of the product. The FDA testing process, from the time the DMSB presents the project's candidate list until the results are received by the DMSB, requires approximately six months.

The FDA will not test all items presented to them as program candidates. The FDA's Center for Biologics Research (CBER) has never permitted the testing of any biological products (vaccines, toxoids, serums, blood products, etc.) in the SLEP. Also, nutritional products and products with a history of poor performance in the SLEP testing process (i.e., water purification tablets and Mefloquine®) are not accepted for testing nor are items where the testing is time and/or cost prohibitive.

The testing conducted by the FDA is comprehensive and scientifically sound. The FDA bases their expiration date extensions on conservative estimates of the useful life of the product as substantiated by the test results. Statistical methods are employed to predict when each

product would be expected to breach the acceptable potency specification, and a date less than that expected breach is chosen. The FDA grants the extensions for all SLEP Participates having the materiel as specified by lot number, expiration date, and manufacturer that has been stored under appropriate conditions. Testing of SLEP products is an ongoing process. Annual or biannual the materiel is retested to confirm extended dating (or even permit further extensions). This is a mandatory requirement for all materiel remaining in the SLEP. Products that fail testing at any time will be destroyed. Products that are not tested or do not receive additional extensions are destroyed upon reaching their final expiration date.

The Current SLEP Process

All pre-positioned and war reserve stocks should be rotated when possible; however, quantities often exceed peacetime requirements. Activities are required to project quantities of products for the program twelve to eighteen months prior to the product's expiration date**.** System wide messages go to all SLEP participants requesting information on products to be entered into future SLEP projects on a routine basis. The U.S. Army Medical Materiel Agency (USAMMA) is currently the Executive Agent for the preparation and dissemination of all FDA/DoD SLEP messages. These are available for viewing at http://www.usamma.army.mil.

Each SLEP Participates evaluates their respective activity's report for items to enter into the FDA/DoD SLEP. Products nominated as candidates for the program are submitted to the DMSB. The DMSB maintains a database of all candidate items, which is used to select products submitted to the FDA for inclusion in an upcoming project. The FDA assigns a project number then sends the list of project products and lot numbers, a list of lot numbers that have been cancelled or not been accepted for projects, and a list of SLEP Participates-specific test item sample requirements to the DMSB. The DMSB then sends the information received from the FDA out to the SLEP Participates for distribution to respective facilities. The FDA requires sample receipt within 60 days of the request. If an item's samples are not received in 60 days, the item is dropped from the project and testing on the samples that were received begins. Timely submission of samples is critical to successful completion of a project.

Upon completion of testing the FDA forwards the results to the DMSB, which forwards them to each SLEP Participates. Any SLEP Participates activity having items with the lot number and expiration date within the realm of the test results may extend specified materiel to the new expiration date only if that materiel has been properly stored in accordance with the manufacturer's specifications. Once a product has been tested it will be re-tested biannually or annually until the product either fails testing or stocks are depleted. Additionally, each fiscal year a list of expired, or soon to expire, drugs is compiled from the DMSB maintained central database to establish new projects in addition to the retest projects carried over from the previous fiscal year.

The direction of the program has changed since its inception. The switch from a large, DoD depot supply system to one supported predominantly by prime vendor suppliers and just-in-time deliveries for day-to-day requirements has refocused the program on pre-positioned stocks and war reserve materiel. The prime vendor system has reduced the need for centrally controlled warehousing of drugs and therefore reduced the pool of products that are eligible for testing.

Additionally, all Medical Treatment Facilities in DoD have the ability to return goods for credit or replacement of expiring stocks of medication in individual facility inventories. Return goods assure replacement of expired products with little or no cost to the facility.

The DoD enjoys a high rate of success with the SLEP because only products known to have a high probability of being extended are included in test projects. Due to the DoD's history and knowledge gained with the program, items with low probability of being extended are not included unless there is a compelling reason for the testing.

Labeling Requirements and Guidance

The FDA requires that product be labeled and relabeled in accordance with the Food, Drug and Cosmetic Act of 1938 (or subsequent amendments) or the Food and Drug Modernization Act of 1997. Products not relabeled in accordance with these laws or FDA regulations are considered misbranded if they are sold, distributed, or dispensed and are in violation of these Acts.

The FDA Center for Drugs (CDER) compliance office recommends the extended product is to be relabeled with the lot number, new expiration date and FDA project number. The new sticker does not have to be the same font and color as the old label. However, the new sticker must not obscure the writing on the original label and the new sticker must be legible. Also, the sticker must adhere to the old label in such a way that if it was peeled off, what was underneath it would also peel off. It is not necessary nor is it advised to remove the original label on a product and put a new label. The FDA does not want the original product label removed. Putting on a new label on the product will require approval by the FDA compliance office. The intent of this is to instill confidence in the ultimate user, that the products they are given or administered are of high quality and safety, and will work effectively as expected.

The FDA has authorized a deferral of the requirement to have every individual unit of issue relabeled only while the materiel is maintained under centralized SLEP Participates control. This was requested in order to reduce the cost for multiple relabeling efforts, as SLEP products may be extended multiple times prior to being issued to individual service members. The FDA will permit SLEP Participates to label only the outer cartons of products with the updated information so long as they remain in centralized storage, control, and management. This materiel must be relabeled completely, down to the individual units of issue, before being distributed/issued to activities or individuals. Due to the requirements for immediate readiness of all SNS drugs, they have opted to relabel all SLEP items immediately after the FDA grants extensions. The Services' medical logistics agencies procure and distribute labels to support the necessary relabeling of SLEP materiel. The DMSB is revising their mode of operations to consolidate this function as well, simplifying the relabeling process and making the SLEP more efficient. The decision to defer or complete relabeling of items will be made by each Service based on the urgency of need for each item and timeline for relabeling in a contingency situation.

Sampling of Data from Items Tested under SLEP

The table provided below represents a number of products tested over several years in the FDA/DoD SLEP.

Table 1. Sample of SLEP Testing History

Product	**Length of Original Dating**	**Average Total Years Extended**	**Total Shelf Life Obtained**
Atropine Sulfate 2mg/ml, 25ml multidose vial	2 years	13 years	15 years
Atropine 2mg/0.7ml Autoinjector	5 years	5 years	10 years
Atropine Sulfate Inhalation Aerosol	4 years	4 years	8 years
Pralidoxime Chloride 600mg/2ml Autoinjector	5 years	13 years	18 years
Pyridostigmine Bromide 30mg tablets	5 years	5 years	10 years
Diazepam 10mg/2ml Autoinjector	4 years	5 years	9 years
Doxycycline 100mg tablets	2 years	5 years	7 years
Ciprofloxacin 500mg tablets	3 years	10 years	13 years
Sodium Nitrite 300mg/10ml vial or ampoule	2 years	8 years	10 years
Sodium Thiosulfate 12.5gm/50ml vial	2 years	14 years	16 years

It is important to note that products tested under this program are maintained under tightly managed, controlled conditions at a limited number of locations. Extrapolation of these data to drugs stored by others would be inappropriate. Storage conditions may vary widely across the population and SLEP data are not generalizable unless storage conditions are identical and verifiable. Even within the SLEP, products known to have been stored under adverse conditions (i.e., high temperature or low temperatures) by SLEP Participates are excluded from the program, unless they are marked and tested separately from “normal” stocks.

Individual prescriptions issued to patients are never considered for extension, even by the SLEP Participates. Items issued to individuals are considered dispensed prescriptions and are never permitted back into the supply chain, regardless of SLEP testing results, since the storage conditions of these items by individuals cannot be assured. Dispensed products that are turned in after completion of an operation are destroyed. Similar practices are executed in routine peacetime care in both DoD facilities and civilian medical practice.

In recent years the value of materiel tested annually in the FDA/DoD SLEP has exceeded $33 million. The cost to for testing of these items has been about $350,000 per year. This gives a rate of return on investment of approximately 94-to-1. Stated differently, for every dollar spent

on the SLEP testing of items the taxpayer has avoided the expenditure of 94 dollars for new, replacement materiel, a very cost-effective use of funds.

The number of drugs being tested has reduced to an average of 13 every year, but the size of the lots, and number of lots of each drug has drastically increased.

This program is a large cost saver to the taxpayer but is only for large stockpiles of medical materiel, or for medical materiel that has limited commercial use (i.e., antidotes for chemical agents). The FDA will not normally test any materiel that has less then $10,000 of a lot on hand by the SLEP Participates. This program is not for the small quantities stocked by most local pharmacies, hospitals or clinics.

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